Sex differences in pharmacological cardioversion in patients with atrial fibrillation

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With an increasing incidence and prevalence worldwide, atrial fibrillation (AF) represents a substantial and growing burden on modern healthcare services [1]. Overall, male patients globally have a higher risk of AF, although one US-based cohort study of 25 119 participants showed that women developed a higher risk of AF incidence when weight and height were controlled, emphasizing the importance of AF treatment in women [2]. The lifetime risk of AF does not appear to be significantly different between men and women [3].

Recent guidelines have moved towards a holistic or integrated care approach to AF management [4, 5]. The latter is now based on the Atrial fibrillation Better Care (ABC) Pathway, and includes avoiding stroke; better symptom and rhythm control with patient-centered decisions on rate or rhythm control, and cardiovascular and comorbidity management, including lifestyle changes [6].

As one option for rhythm control (the 'B' in the ABC pathway), pharmacological cardioversion serves as a safe and efficacious method to restore sinus rhythm and control symptoms without sedation in hemodynamically stable patients after consideration of the thromboembolic risk [4]. Antiarrhythmic drugs (AAD) are often used for pharmacological cardioversion and can also enhance the effectiveness of electrical cardioversion [7]. According to guidelines, AAD options for cardioversion include oral or intravenous flecainide, oral or intravenous propafenone, intravenous vernakalant, intravenous amiodarone, and intravenous ibutilide [4]. Other studies have provided evidence that antazoline, the first-generation antihistamine included in this study, demonstrates some effectiveness in facilitating cardioversion [8].

The study based on CANT-II registry by Wybraniec et al. [8], which included 1365 short-duration AF patients, aimed to compare sex differences on the effect and safety of pharmacological cardioversion. Female patients were more symptomatic, had higher CHA_2DS_2-VASc scores, and greater prevalence of tachyarrhythmia compared to men.

Sex differences exist in the frequency of AAD use. In the study by Wybraniec et al, more female than male patients were treated with amiodarone, while class Ia AAD antazoline was more frequently used in males, compared with females. In a report from the EORP-AF study, females were more likely to have pharmacological cardioversion (28.2% vs. 22.4%), less likely to receive rhythm control, and more likely to receive rate control, compared to men [9].

Sex differences also exist in the efficiency of AAD. Wybraniec et al. [8] reported that the use of amiodarone or propafenone was associated with cardioversion failure in males, and propafenone has a significantly lower rate of rhythm conversion in males. The success rates and safety of antazoline, as a single AAD, were comparable in both sexes. In a prospective single-center study conducted in the years 2011–2013, female sex showed an association with success of pharmacological cardioversion [10]. Park et al. [11] also found that females after catheter ablation demonstrated a better AAD response after AF recurrence. In the

Finnish CardioVersion study, female sex was reported as one of the independent predictors (odds ratio, 2.1; 95% confidence interval, 1.1–4.0) of thromboembolism within 30 days after cardioversion [12]. In addition, women showed higher cardiovascular mortality and morbidity after rhythm control treatment. Severe adverse effects of AAD were also more common in female patients enrolled in the RACE study [13]. Quality of life under rhythm or rate control treatment generally remained worse for female patients than males after 12 months [13]. In one single-center retrospective study, vernakalant was more effective than flecainide among males (65.2% vs. 36.9%), while no significant differences were found in females [14]. Female sex was linked to higher rate of sinus rhythm restoration (80% vs. 58%), in contrast to men, when using intravenous vernakalant for recent-onset AF [15].

In conclusion, sex differences are evident in drug therapy for AF rhythm control, in terms of medication selection, efficacy, and safety. It would be important to note that safety profiles of different AADs also vary between males and females. Nonetheless, AADs (and rhythm control) are but one part of the holistic care for AF patients. No significant sex differences in outcomes were reported in the prospective mAFA-II trial comparing the ABC pathway versus the usual care [16]. Sex differences in stroke risk associated with AF are also the subject of interest given that female sex is a stroke risk modifier incorporated into the CHA_2DS_2-VASc score [17]. Apart from sex, clinical complexity phenotypes in AF patients can impact outcomes, even in relation to adherence to the ABC pathway [18, 19]. Further studies reporting sex differences in AF management are needed, perhaps with the goal of better personalized treatment decision-making.

Article information

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